Review Article

Impact of adherence to WHO infant feeding recommendations on later risk of obesity and non-communicable diseases: systematic review

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Abstract

Adherence to WHO infant feeding recommendations has short-term benefits and may also help in the prevention of non-communicable diseases (NCDs). This study reviewed the evidence on whether adherence to all elements of the WHO infant feeding recommendations (comparison group those exclusively breastfed to 6 months, introduced to appropriate complementary feeding from 6 months, with continued breastfeeding to at least 24 months; exposure group characterised by non-adherence to any of the three recommendations) is associated with reduced risk of later obesity or cardiometabolic disease. The population of interest was children not classified as very low weight (weight-for-age z -score >-3.0). MEDLINE, EMBASE, Global Health, CINAHL plus, ProQuest Dissertations and Thesis were systematically searched from 2001 to July 2014, manual reference searching of a birth cohort register (<http://www.birthcohorts.net/>) as well as papers identified in the search and selected journals was carried out. The database search yielded 9050 records, 275 English-language full-text articles were screened, but no studies were eligible, failing to meet the following criteria: comparison (213); exposure (14); population (3); relevant outcome (5); outcome before 24 months (9); insufficient information provided (30); plus one study was qualitative. Eight studies met the inclusion criterion of exclusive breastfeeding to 6 months, but did not meet the other inclusion criteria. The present study has revealed an important gap in the evidence on NCD prevention, and suggestions for addressing this evidence gap are provided.

Keywords: obesity NCDs, infant feeding, complementary feeding, exclusive breastfeeding, breastfeeding.

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Introduction

Since 2001, the WHO has recommended that infants are breastfed exclusively to the age of 6 months, and that appropriate complementary feeding should be introduced at 6 months with continued breastfeeding to 2 years (World Health Organization and UNICEF 2003). These recommendations are based on evidence largely from studies of the short-term health outcomes of infant feeding (World Health Organization

and UNICEF 2003). Across the globe, these infant feeding recommendations are the focus of many public health policies, targets and investments.

Breastfeeding has important benefits over artificial feeding in the short term, notably reduced risk of infectious disease (particularly diarrhoea and pneumonia; PAHO/WHO 2002), and this is true even in settings where hygiene is considered adequate (Howie *et al.* 1990; Kramer *et al.* 2001). Breast milk should be an important source of nutrients beyond 6

months. Complementary feeding is often problematic in terms of nutrient adequacy, or in terms of increased exposure to pathogens in water supplies. In the longer term, compliance with individual elements of the WHO infant feeding recommendations, exclusive breastfeeding in particular, appears to be important to reduce later risk some non-communicable diseases (NCDs) and obesity, as identified by previous systematic reviews (Horta *et al.* 2007; Monasta *et al.* 2010). There is less evidence on the long-term impact on NCD risk of appropriate complementary feeding, or of continued breastfeeding to 24 months or beyond. However, systematic reviews suggest that increasing the 'dose' of breastfeeding by extending breastfeeding duration is likely to reduce later risk of obesity and obesity-related NCDs (Horta *et al.* 2007; Yan *et al.* 2014). However, previous reviews did not focus on the long-term health impact of compliance with all elements of the infant feeding recommendations, an important global public health question in the context of NCD and obesity prevention.

The present study was concerned with the adherence to all three principal WHO infant feeding recommendations: exclusive breastfeeding to 6 months; introduction of nutritionally adequate and safe complementary feeding from 6 months; with continued breastfeeding to 24 months or beyond. The extent to which compliance with all three WHO infant feeding recommendations (comparison group), compared to non-compliance, might influence longer term health outcomes is unclear.

In order to address this possible gap in the evidence, the WHO Department of Maternal, Newborn,

Child and Adolescent Health commissioned a systematic review and formal quality appraisal of the evidence (to be carried out by the current authors) on the long-term health impact of compliance with all of the WHO infant feeding recommendations in 2014. The review and appraisal was intended to provide the basis of a more evidence-informed approach to using infant feeding policy in global NCD and obesity prevention in future. The aims of this paper are to review systematically the available evidence on this topic, to critique the evidence, and to suggest ways in which the evidence base might be improved quickly in order to address this important global public health issue.

Methods

Research question

The research question was: in infants and children aged 6–24 months who are classified by the Integrated Management of Childhood Illness (Handbook IMCI 2005) as 'not very low weight' (weight-for age ≥ -3 z-score), what is the effect of (a) stopping exclusive breastfeeding before the age of 6 months, (b) not breastfeeding, (c) introducing complementary foods before the age of 4 months or 6 months, (d) stopping breastfeeding before the age of 12 or 24 months, compared with following all of the WHO infant feeding recommendations, on the risk of becoming overweight/obese, developing cardio-metabolic risk factors or developing cardiovascular diseases or diabetes mellitus type 2 in later life?

Key messages

- Greater adherence to WHO infant feeding recommendations may be important in preventing NCDs globally in the future.
- At present, there is limited evidence linking adherence to all WHO infant feeding recommendations (exclusive breastfeeding to 6 months, introduction of appropriate complementary feeding from 6 months, continued breastfeeding to at least 24 months), vs. non-adherence, to later risk of obesity and cardiometabolic disease.
- Of the 275 papers identified for full-text screening, none were eligible for inclusion, with most (213) not having an appropriate comparison group (which adhered to all three WHO infant feeding recommendations).
- There is an urgent need for more evidence on associations between adherence to all WHO infant feeding recommendations and long-term health outcomes.
- Greater emphasis on existing cohort studies, particularly those in low- and middle-income countries, could help address this evidence gap relatively quickly.

Literature searching

Since the recommendation for exclusive breastfeeding up to 6 months of age and continued breastfeeding for up to 2 years was published in 2001 (World Health Organization and UNICEF 2003), studies published from 2001 were eligible for inclusion. MEDLINE, EMBASE, Global Health, CINAHL plus, ProQuest Dissertations and Thesis were systematically searched from 2001 to July 2014, and manual reference searching of a birth cohort register (<http://www.birthcohorts.net/>) as well as papers identified in the search. We also searched the Bulletin of the WHO in PubMed Central and manually searched the *South East Asian Journal of Public Health* because of its relevance to the topic and because it is not indexed in the databases searched. Keywords were searched as subject headings indexed in databases and as free-text terms. Booleans were used to refine the search. Controlled vocabulary and search syntax were modified as appropriate when searching databases. The search strategy in Medline (ovid) is given in Fig. 1. Details of the search strategies for the other databases searched are available from the corresponding author on request.

Study eligibility criteria

The types of studies eligible for inclusion in this review were cross-sectional studies; case-control studies; retrospective and prospective longitudinal studies; case-series; non-randomised controlled trials; randomised controlled trials. Eligible for inclusion were studies that provided data for infants and children aged 6–24 months classified by IMCI as not very low weight, namely weight-for-age ≥ -3 z-scores.

Eligible for inclusion in this review were the following intervention conditions/exposures: stopping exclusive breastfeeding before the age of 6 months, not breastfeeding, introducing complementary foods before the age of 4 months or 6 months, stopping breastfeeding before 12 or 24 months. The eligible comparison condition was the requirement to meet all WHO infant feeding recommendations: exclusive breastfeeding from birth to 6 months, introducing complementary foods at 6 months of age, with continued breastfeeding until 24 months of age.

We intended to include studies with outcomes that were measures of adiposity (body fatness), or proxies for adiposity (e.g. BMI or BMI z-score, waist circumference or waist circumference z-score). Measures of overweight and obesity were to be included if they reported odds ratio of at least one of the following measures comparing intervention/exposure condition with comparison condition: classification of overweight <5 years of age: BMI standard deviation score >2 ; classification of overweight 5–19 years of age: BMI z-score >1.04 – 1.63 , BMI percentile 85th–94.9th relative to suitable reference population; classification of overweight ≥ 19 years: BMI 25 – 30 kg m $^{-2}$; classification of obesity <5 years of age: BMI standard deviation score >3 ; classification of obesity 5–19 years of age: BMI z-score ≥ 1.64 , BMI percentile ≥ 95 th relative to suitable reference population; classification of obesity ≥ 19 years: BMI ≥ 30 kg m $^{-2}$. The following measures of risk factors for cardiovascular disease or diabetes mellitus type 2 were considered for inclusion in this review: blood pressure: group means and mean difference (in mmHg) in systolic and diastolic blood pressure; fasting blood glucose levels: group means or mean difference in mmol L $^{-1}$ or mg dL $^{-1}$; impaired glucose tolerance: odds ratio comparing intervention/exposure condition with comparison condition; elevated glycosylated haemoglobin (HbA1c) levels: odds ratio comparing intervention/exposure condition with comparison condition; Insulin levels: group means or mean difference in mmol L $^{-1}$ or mg dL $^{-1}$; insulin resistance: odds ratio comparing intervention/exposure condition with comparison condition; Total blood cholesterol levels: group means or mean difference in mmol L $^{-1}$ or mg dL $^{-1}$; Blood triglycerides levels: group means or mean difference in mmol L $^{-1}$ or mg dL $^{-1}$; Blood lipoprotein levels (low-density lipoprotein – LDL, high-density lipoprotein – HDL): group means or mean difference in mmol L $^{-1}$ or mg dL $^{-1}$; composite scores for cardiometabolic risk which included some or all of the above indicators. Eligible measures of cardiovascular events were limited to odds ratio of angina pectoris (chest pain), stroke, myocardial infarction, and mortality. Odds ratio of diabetes mellitus type 2 defined/diagnosed according to the WHO criteria comparing

1. 1. Infant/
2. 2. (infant or newborn or toddler).tw.
3. 3. infancy.tw.
4. 4. 1 or 2 or 3
5. 5. exp Infant Food/ or exp Infant Formula/
6. 6. exp Breast Feeding/
7. 7. exp Milk, Human/
8. 8. exp Weaning/
9. 9. exp Bottle Feeding/
10. 10. (breast adj2 (feeding or fed or milk)).tw.
11. 11. breastfeeding.tw.
12. 12. ((exclusive or partial or predominant or continued) adj1 breastfeeding).tw.
13. 13. (bottle adj2 (feeding or fed)).tw.
14. 14. (formula adj2 (feeding or fed or milk)).tw.
15. 15. ((infant or child) adj2 feeding).tw.
16. 16. weaning.tw.
17. 17. complementary food*.tw.
18. 18. or/5 - 17
19. 19. exp Obesity/ or exp Overweight/ or exp Body Weight/
20. 20. exp Body Mass Index/
21. 21. exp Adiposity/
22. 22. exp Body Height/
23. 23. (overweight or over weight or over-weight).tw.
24. 24. obes*.tw.
25. 25. "body mass index".tw.
26. 26. "BMI".tw.
27. 27. "weight-for-height".tw.
28. 28. or/19 - 27
29. 29. exp Blood Pressure/
30. 30. *Hypertension/
31. 31. ((systolic or diastolic) adj1 blood pressure).tw.
32. 32. exp Cholesterol, HDL/ or exp Cholesterol/ or exp Cholesterol, LDL/
33. 33. exp Dyslipidemias/
34. 34. dyslipid?mia.tw.
35. 35. hypercholesterol?mia.tw.
36. 36. ((low or high) adj1 density lipoprotein).tw.
37. 37. cholesterol.tw.
38. 38. exp Blood Glucose/
39. 39. exp Hyperglycemia/
40. 40. exp Glucose Intolerance/
41. 41. "glucose intolerance".tw.
42. 42. exp Insulin/
43. 43. exp Insulin Resistance/

Fig. 1. Search strategy in Medline (ovid).

44. 44. exp Hyperinsulinism/
45. 45. hyperglyc?mia.tw.
46. 46. hyperinsulin?mia.tw.
47. 47. hyperlipid?mia.tw.
48. 48. insulin resistance.tw.
49. 49. exp Hemoglobin A, Glycosylated/
50. 50. HbA1c.tw.
51. 51. ((glycated or glycosylated) adj1 h?moglobin).tw.
52. 52. or/29 - 51
53. 53. exp Diabetes Mellitus, Type 2/
54. 54. diabetes mellitus.tw.
55. 55. ((type 2 or type two or type II) adj1 diabetes mellitus).tw.
56. 56. exp Cardiovascular Diseases/
57. 57. exp Myocardial Infarction/
58. 58. exp Stroke/
59. 59. exp Mortality/
60. 60. myocardial infarct*.tw.
61. 61. heart attack.tw.
62. 62. exp Angina Pectoris/
63. 63. angina pectoris.tw.
64. 64. chest pain.tw.
65. 65. stroke.tw.
66. 66. cerebro-vascular event.tw.
67. 67. mortality.tw.
68. 68. fatal.tw.
69. 69. death.tw.
70. 70. or/53 - 69
71. 71. 28 or 52 or 70
72. 72. 4 and 18 and 71
73. 73. exp Infant, Very Low Birth Weight/
74. 74. 72 not 73
75. 75. exp animal/ not human/
76. 76. 74 not 75
77. 77. limit 76 to (english or german)
78. 78. limit 77 to yr="2001 -Current"
- 79.

Fig. 1. Continued

intervention/exposure condition with comparison condition were also included as an outcome.

Data collection, extraction and plans for data analysis and synthesis

Two authors (AM and AC) independently screened and cross-checked titles and abstracts to identify potentially relevant studies based on the study inclusions and exclusion criteria described above. Where possible, full-text reports of potentially relevant studies were obtained, and assessed independently by two authors (AM, JJR), with discrepancies resolved by discussion and the opinions of a third author (RMB).

Methods planned for study data extraction, quality assessment and synthesis are given in Table 1.

Results

Figure 2 shows the results of the literature search. The electronic database search yielded 9050 records. Five additional records were identified through screening of reference lists of reviews. After discharge of 1237 duplicates, 7818 titles and abstracts were screened by AM and AC. Of these, 303 records were selected for full-text screening; however, 25 records were available as abstracts only and three records were not available in the English language, and thus were excluded from further assessment. None of the independently screened (AM, JJR) 275 full-text articles met the inclusion criteria described above.

The majority of excluded records ($n = 213/275$) did not meet the combined comparison criterion, that is exclusive breastfeeding for 6 months, introduction of complementary feeding from 6 months and continuous breastfeeding up to 24 months. Of the 275 papers selected for full-text screening, 50 used the WHO definition of exclusive breastfeeding, 40 used some alternative definition of exclusive breastfeeding (typically including intake of water or tea), and the remainder did not clarify how exclusive breastfeeding was defined. Suggested ways of improving the literature in the future, so that it addresses the research question asked by the present study, are given below.

Only eight studies evaluated the effect of exclusive breastfeeding for at least 6 months on later risk of either obesity or NCDs compared to other types of infant feeding (Kramer *et al.* 2003, 2009; Rapp *et al.* 2005; Moschonis *et al.* 2008; Simon *et al.* 2008; Franklin 2013; Hunsberger *et al.* 2013; Urban 2013). However, these studies failed to report whether continuous breastfeeding occurred up to 24 months (Table 2). Other reasons for exclusion were that studies did not meet the exposure (infant feeding other than WHO recommendation), population or outcome criteria or reported outcomes when children were younger than 24 months. For 58 records, no decision could be made due to insufficient reporting and one article reported data from interviews only (a qualitative study).

Discussion

While no studies were eligible, the search and screening process in the present study identified a number of studies, which may potentially have had data to answer the research question, but which did not report the appropriate comparison for the research question asked by the present review. Among the 213 papers rejected on the grounds of not presenting relevant comparison data as they focused on different comparisons and research questions, some may have collected (but not reported) data that could be reanalysed to address the comparison of long-term health impact of compliance with the WHO infant feeding recommendations (vs. non-compliance). For the eight studies that identified groups of infants fed exclusively to 6 months according to the WHO definition (Table 2), it might be possible to ask a different research question, concerning the impact of adherence to this recommendation alone on later risk of NCDs. There may also be evidence that addresses the research question posed by the present review, but in a different population to that considered by the present review (specifically, in the very low birth weight).

In the absence of published English-language evidence that addressed our research question, a critique of the evidence and its reporting, identified in our systematic review, may encourage future studies to address this important global health question.

Table 1. Plans for data extraction, data analysis and synthesis

Data extraction	<p>We planned to use separate standardised protocols for the research question for extracting relevant information from the studies. Data extraction was to be performed by at least two reviewers, extracts to be compared in meetings, and discrepancies resolved through discussion.</p> <p>The following items were to be extracted from eligible studies:</p> <p>General study information: study ID (first author and year of publication), type of publication, details of corresponding author, funding source</p> <p>Eligibility criteria: study design, population, intervention/exposure, comparison, outcome, reason for exclusion</p> <p>Population: inclusion/exclusion criteria, number of participants recruited, included in analyses and followed; attrition rates; methods and setting for recruitment; year of birth, study location (country; low-income country, high-income country), gender, birth weight</p> <p>Intervention/exposure: type of feeding condition, duration of feeding condition, length of recall, source of information (records, participant, mother)</p> <p>Outcomes: type of overweight/obesity measure, type of cardio-metabolic risk factor, type of cardiovascular event, follow-up time points (age at outcome assessment)</p> <p>Results: continuous and dichotomous summary statistics, mean differences, control for confounding and/or mediating variables</p>
Quality assessment of studies	<p>Quality of included studies was to be independently assessed by authors AM and JJR, cross-checked and discussed to resolve disagreement where required. We planned to use the risk of bias assessment tool from the Agency for Health Care and Quality (Vishwanathan <i>et al.</i> 2013).</p>
Assessment of heterogeneity	<p>We intended to assess heterogeneity of findings by comparing similarity of included studies in terms of study design (e.g. prospective study, cross-sectional study), setting (e.g. high- or low-income country), participants (e.g. year of birth), interventions/exposure (e.g. length of recall, source of information, categories of breastfeeding), outcomes, consideration of confounding, and study quality. Additionally, we will evaluate cause of heterogeneity by conducting subgroup and sensitivity analyses (see below).</p>
Assessment of publication bias	<p>If the number of included studies allowed (≥ 10 studies), we aimed to assess reporting bias by using a funnel plot that assists evaluating the association between effect size and standard error. An asymmetric plot may indicate publication bias or a real relationship between study size and effect size, as when larger studies have lower compliance rates and compliance is positively related to effect size.</p>
Data synthesis	<p>We intended to use Review Manager 5.3 for data analysis. Studies unsuitable to be included in a meta-analysis were to be described narratively. Studies reporting similar outcome measures were to be combined in a meta-analysis. We aimed to pool effect estimates using random-effect models to account for heterogeneity between studies. Effect estimates were to be reported as (i) weighted mean differences and their 95% confidence interval (CI) for continuous outcomes, (and ii) pooled odds ratios and 95% CI for dichotomous outcomes. For the continuous outcomes, a negative mean difference denotes a lower value among participants who were exclusively breastfed from birth to 6 months of age and continued to be breastfed until 24 months. For dichotomous outcomes, an odds ratio < 1 denotes that exclusive breastfeeding up to 6 months of age and continued breastfeeding until 24 months is associated with lower odds of the outcome. Estimates of effects will be summarised in the GRADE Evidence Profiles along with the quality rating of the evidence where appropriate.</p>
Quality assessment of evidence	<p>To assess and grade the quality of the evidence for each outcome (high, moderate, low, very low), we will use the GRADEpro software.</p>
Subgroup analysis	<p>Subgroup analyses were principally intended to investigate sources of heterogeneity within a meta-analysis in relation to factors that potentially impact on outcomes. If the number of included studies allows, subgroup analyses within this review were to focus on the following items:</p> <p>Age group (≤ 9 months, 5–10 years, 11–19 years, > 19 years)</p> <p>Study size (< 500 participants, 500–1499 participants, ≥ 1500 participants)</p> <p>Study design (randomised, non-randomised, cohort, case-control, cross-sectional)</p> <p>Control of confounding (none, adjusted for socio-economic status, also adjusted for birth condition, also adjusted for parental anthropometry)</p> <p>Setting (low-income country, high-income country)</p>
Sensitivity analysis	<p>We intended to investigate the influence of study characteristics on the robustness of the review results by conducting sensitivity analyses. We will remove trials from the analysis and perform a re-analysis with the remaining studies when studies are judged to be at 'high-risk' of bias.</p>

Fig. 2. Literature search for studies comparing adherence to WHO infant feeding recommendations vs. non-adherence on long-term outcomes of obesity and NCD risk factors.

Existing cohort studies may well have data that would address the research question we posed. Future studies could also address the research question we asked by attending to a number of the weaknesses in the literature identified by the present study. First, future studies should provide clearer descriptions of infant and early child feeding of study participants, and should categorise infant feeding groups using the WHO definitions of breastfeeding (exclusive, predominant, partial) and complementary feeding: as noted above, even recent studies commonly categorized feeding using definitions other than the WHO definitions, or failed to define the infant feeding categories used.

Future studies should also provide clearer descriptions of whether the same mothers adhering to feeding recommendations at later time points (e.g. 18–24 months) are those adhering to recommendations at earlier time points (e.g. exclusive breastfeeding up to 6 months). It would also be useful to determine whether or not any effects of following infant feeding recommendations are cumulative (i.e. the longest duration of exposure is most beneficial), or whether or not there are particular periods in

infancy and early childhood where adherence to infant feeding recommendations might have greater benefits for long-term NCD or obesity prevention. It would also be useful if future studies were able to characterise the energy content and macronutrient composition of the complementary feeding diet as these variables are likely to be important to future risk of obesity (Ong *et al.* 2006).

Finally, in many of the published studies ineligible for the present review, the numbers of study participants actually complying with WHO infant feeding recommendations appeared to be very low, too low to address the research question. This lack of numbers of participants probably reflects a bias in the literature towards western populations. While still suboptimal, many understudied non-Western populations have higher levels of adherence to all of the WHO infant feeding recommendations up to 24 months (Gupta *et al.* 2013; Lutter & Morrow 2013): high prevalence of exclusive breastfeeding to 6 months; appropriate complementary feeding from 6 months while continuing breastfeeding to 24 months. A greater focus on studies of such populations, including future secondary analyses of existing cohort data, could address this

Table 2. List of studies comparing children exclusively breastfed for 6 months with children exposed to other types of infant feeding

Study ID	Cohort	Exposure	Comparison	Outcome
Franklin 2013	Kansas Special Supplementary Nutrition Program for Women, Infants, and Children (WIC)	Exclusively breast fed ≥ 6 months	Never excl. breastfed	Overweight/obesity
Hunsberger <i>et al.</i> 2013	IDEFICS study	Exclusively breast fed 4–6 months, 7–12 months	Never excl. breastfed	Overweight Waist top hip ratio Weight-for-length z-scores BMI, Waist circumference, Fat mass, Blood pressure
Kramer <i>et al.</i> 2003	PROBIT trial	Exclusively breast fed ≥ 6 months	3 months excl. breastfed	Overweight/obesity
Kramer <i>et al.</i> 2009	PROBIT trial	Exclusively breast fed ≥ 6 months	3 months excl. breastfed	Overweight/obesity
Moschonis <i>et al.</i> 2008	Greek preschoolers	Exclusively breast fed ≥ 6 months	Excl. formula fed	Metabolic dysfunction includes HDL, LDL, triglycerides, blood pressure, HOMA-IR, WHR
Rapp <i>et al.</i> 2005	German preschoolers	Exclusively breast fed > 6 months	Excl. breastfed < 2 months	
Simon <i>et al.</i> 2008	Brazil: children aged 2–6 years	Exclusively breast fed > 6 months	Excl. breastfed < 6 months	
Urban 2013	USA: obese children/adolescents aged 8–17 years	Exclusively breast fed ≥ 6 months	Unclear: excl. breastfed < 3 months and/or 3– < 6 months	

important research question in future. However, while a greater focus on populations in low- and middle-income countries might provide an answer to the research question posed by the present review, the generalizability of that answer to high-income countries would need to be considered carefully.

Conclusion

In summary, the present review has identified major gaps in both evidence quality and quantity, and fundamental weaknesses in reporting of evidence on the question of the long-term health impact of compliance with all WHO infant feeding recommendations. Compliance with infant feeding recommendations may well have important implications for global obesity and NCD prevention, and further studies in this area are required urgently. We have provided a number of suggestions to increase the quality and quantity of evidence on the long-term public health impact of compliance with WHO infant feeding recommendations, and would welcome greater attention to this topic in the future as part of the global response to obesity and NCD prevention.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

Original concept: all authors and WHO; study design: all authors; searching and initial screening: AM and AC; full text screening: AM, JJR and RMB; drafting of manuscript: AM and JJR; critical review and writing of manuscript: all authors.

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